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(54) MIXED LIPIDIC MEMBRANE VESICLE

(57)Abstract:

PURPOSE: To obtain a mixed lipidic vesicle produced from a phospholipid and a nonionic polyoxyethylenic surfactant at a specific ingredient ratio with hardly any dispersion in particle diameter.

CONSTITUTION: This O/W/O type mixed lipidic vesicle is obtained by ultrasonically treating a mixed lipid of a phospholipid with a nonionic polyoxyethylenic surfactant at (5/95) to (95/5) molar ratio and has 100-3000 Åparticle diameter and ≤10% dispersion thereof. Thereby, the particle diameter can be controlled according to the kind and amount of the medicine enclosed in the vesicle or the purpose.

LEGAL STATUS

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* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1] The O/W/O mold mixing lipid membrane vesicle of 10% or less of dispersion of the particle size of 100-3000A, and particle size obtained when the mole ratio of phospholipid and a nonionic polyoxyethylene system surfactant ultrasonicates the mixed lipid of 5 / 95 - 95/5 in a water solution

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention relates to the lipid membrane vesicle used for drugs embedding or cosmetics material embedding.
[0002]
[Description of the Prior Art] Before, it is evaluated noting that liposome (O/W/O mold lipid membrane vesicle) is known well and it is useful to a drug delivery system as a closing vesicle using phospholipid or phospholipid, and cholesterol. There is several sorts of liposome, such as multiplex layer liposome and one-sheet film liposome, among the liposome, and some manufacture approaches, such as an opposition evaporation method, the stirring method, and an ultrasonic wave method, are learned.
[0003]
[Problem(s) to be Solved by the Invention] Since said approach used the solvent at the time of liposome manufacture, it had problems, such as the residual toxicity. Therefore, the heating dissolution of the water-soluble polyhydric alcohol and phospholipid in which living body administration is possible is carried out, and there is a manufacturing method (JP,60-7932,A) of the liposome by stirring underwater. Although this approach uses polyhydric alcohol, such as glycerol, as a non-volatile solvent, polyhydric alcohol itself was difficult not to become a membrane component but to save with a uniform particle size for a long period of time.
[0004] Moreover, in the case of liposome, in order to arrange particle size, gel **** etc. needed to be operated complicated.
[0005] The purpose of this invention is offering a lipid membrane vesicle with a uniform particle size stable for a long period of time.
[0006]
[Means for Solving the Problem] This invention is an O/W/O mold mixing lipid membrane vesicle of 10% or less of dispersion of the particle size of 100-3000A, and particle size obtained when the mole ratio of phospholipid and a nonionic polyoxyethylene system surfactant ultrasonicates the mixed lipid of 5 / 95 - 95/5 in a water solution.
[0007] The phospholipid used by this invention is phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, soybean phosphatide, yolk phospholipid, etc. Nonionic polyoxyethylene system surface active agents are polyoxyethylene sorbitan fatty acid ester (tween20: ARUTASU powder company make etc.), polyoxyethylene alkyl phenyl ether (tritonX100: made in loam & Haas etc.), etc.
[0008] In this invention, the mole ratios of phospholipid and an oxyethylene system surfactant are 5 / 95 - 95/5. Except the range of the above [the mole ratio of phospholipid and a nonionic polyoxyethylene system surfactant], in sonication in an aquosity solvent, it becomes opaque dispersion liquid, or it is not only hard coming to come out repeatability at mixed lipid membrane vesicle creation time at particle size, but will be in a micell condition, and the lipid membrane vesicle made into the purpose will not be obtained.

[0009] The mixed lipid membrane vesicle of this invention is obtained when the mole ratio of phospholipid and a nonionic polyoxyethylene system surfactant ultrasonicates the mixed lipid of 5 / 95 - 95/5 in a water solution. Water solutions are distilled water, a phosphate buffer solution, a physiological saline, etc.
[0010] The lipid membrane vesicle of this invention can be obtained by ultrasonicating with the ultrasonic output of 50-100W for 10 - 30 minutes above the phase transition temperature of for example, a mixed lipid.
[0011]
[Effect of the Invention] Dispersion in the particle size generated in the specific mole ratio of phospholipid and a nonionic polyoxyethylene system surfactant is a mixed lipid membrane vesicle stable small for a long period of time, and this invention can control particle size according to the class, amount, or the purpose of the drug which carries out embedding into a vesicle. For example, particle size can be enlarged in order to make particle size small in order to lessen that phagocytosis is carried out to a macrophage, when a medicine is prescribed for the patient into blood, or to carry out embedding of the drug in large quantities into a lipid membrane vesicle. Moreover, actuation of gel **** for arranging the particle size which is needed in the case of a lipid membrane vesicle etc. is not needed.
[0012]
[Example]
(An example 1, example 1 of a comparison) It blended at a rate which showed the mixed lipid of JIRAU roil phosphatidylcholine (DLPC) and tritonX100 in Table 1, output 50W were ultrasonicated for 30 minutes in 50ml of 0.01M phosphate buffer solutions of PH7.4 of 25-degreeC, and the mixed lipid membrane vesicle was obtained. Particle size was measured by dynamic light scattering. The result was shown in Table 1.
[0013]
[Table 1]

	DLPC/tritonX100 (モル比)	1日目の粒径 (オングストローム)	30日目の粒径 (オングストローム)
実施例1	90／10	400±25	430±25
	80／20	330±20	350±25
	65／35	800±50	850±55
	40／60	150±15	150±15
	30／70	110±10	110±10
	10／90	100±10	100±10
比較例1	100／0	不透明分散液	凝集
	97／3	不透明分散液	凝集
	3／97	ミセル状態	ミセル状態
	0／100	ミセル状態	ミセル状態

DLPC＝10^{-3}M

[0014] According to the presentation ratio of DLPC and tritonX100, the mixed lipid membrane vesicle of various particle size was obtained, also after 30 days, the same particle size was maintained and the very stable mixed lipid membrane vesicle was formed. On the other hand, in the case of the example of a comparison, it changed into opaque dispersion liquid or a micell condition, and a mixed lipid membrane vesicle was not formed.

[0015] (An example 2, example 2 of a comparison) The lipid membrane vesicle was made to form according to an example 1 except having made it the combination which showed the mixed lipid of DLPC and tween20 in Table 2.

[0016]

[Table 2]

	DLPC/tween20 （モル比）	1日目の粒径 (オングストローム)	30日目の粒径 (オングストローム)
実施例2	90／10	2500±100	2700±100
	65／35	2300±100	2500±130
	40／60	990± 50	1050± 70
	30／70	830± 50	910± 50
	20／80	480± 35	520± 50
	10／90	400± 35	450± 40
比較例2	97／3	不透明分散液	凝集
	3／97	ミセル状態	ミセル状態
	0／100	ミセル状態	ミセル状態

DLPC=10^{-3}M

[0017] 30 days after maintained the same particle size, and the very stable mixed lipid membrane vesicle was formed. On the other hand, in the case of the example of a comparison, it changed into opaque dispersion liquid or a micell condition, and a mixed lipid membrane vesicle was not formed.
[0018] (An example 3, example 3 of a comparison) The mixed lipid membrane vesicle was made to form according to an example 1 except having made it the combination which showed the mixed lipid of JIRINORE oil phosphatidylcholine (DLoPC) and tritonX100 in Table 3.
[0019]
[Table 3]

	DLoPC/tritonX100 (モル比)	1日目の粒径 (オングストローム)	30日目の粒径 (オングストローム)
実施例3	90／10	500±50	500±50
	80／20	530±50	550±50
	65／35	630±55	660±55
	40／60	970±70	1150±85
	30／70	720±60	800±70
	15／85	350±30	350±30
	10／90	300±30	300±30
比較例3	97／3	不透明分散液	凝集
	3／97	ミセル状態	ミセル状態

DLoPC＝10^{-3}M

[0020] The very stable hybrid lipid membrane vesicle at which 30 days after maintained the same particle size was formed. On the other hand, in the case of the example of a comparison, it changed into opaque dispersion liquid or a micell condition, and a mixed lipid membrane vesicle was not formed.

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